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Impact of infectious and inflammatory disease on cytochrome P450-mediated drug metabolism and pharmacokinetics

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Abstract

Infection and inflammation are associated with down-regulations of hepatic and extrahepatic cytochrome P450s, as well as other drug metabolizing enzymes and transporters. We will review the genesis of inflammatory reactions, and discuss the relevance of the inflammatory regulation of P450 enzymes observations to clinical drug-disease and drug-drug interactions. Mechanistically, understanding the enzyme specificity and mechanisms of regulation will allow us to make better decisions about drug dosage regimens when a patient's inflammatory status changes.

Keywords

drug metabolism; pharmacokinetics; inflammation; infection; cytokines; biologics

Theoretically, infectious or inflammatory disease states can modulate drug pharmacokinetics via several mechanisms. The two major organs of drug clearance are the liver and the kidneys, and alterations in blood flow to these organs will decrease their clearance rates. The liver is the most important site of metabolism clearance, and so changes in the activities or expression of drug metabolizing enzymes have the potential to alter hepatic clearance, for drugs whose clearance is not blood-flow limited. Alterations in drug transporters and drug metabolizing enzymes in the liver or the epithelial cells of the small intestine due to inflammation or infection also have the potential to affect oral bioavailability. The majority of drugs are eliminated via hepatic cytochrome P450 (P450) -dependent metabolism, and so this article will concentrate on the regulation of cytochrome P450 enzymes in inflammatory disease states. Readers are referred to an excellent recent review for a discussion of the impact of inflammatory disease states on drug transporters (1).

CHARACTERISTICS OF INFECTIOUS AND INFLAMMATORY DISEASES

Inflammation is caused by the activation of the innate immune system in response to tissue damage or infectious agents. In infection the innate immune system is activated by microbial molecular patterns via receptors such as the toll-like receptor (TLR) or nucleotide-binding oligomerization-domain protein (NOD) families (2). Tissue damage (e.g. necrosis) often results in the abnormal localization of cellular components that are recognized by molecular sensors such as the inflammasome (cytoplasmic protein complexes containing NOD-like receptor family proteins). Activation of TLRs, NODs or inflammasomes triggers the release of inflammatory mediators that regulate target cells for elimination of microbes or function in tissue repair. Inflammatory mediators include proinflammatory cytokines, vasoactive

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amines such as histamine, peptides such as bradykinin, and lipid mediators like prostaglandins (2).

The liver responds to inflammatory signals with the increased synthesis and secretion of a battery of acute phase proteins (APP), including fibrinogen, α_1 -acid glycoprotein and C-reactive protein, which are involved in homeostasis (3). Because proinflammatory cytokines such as interleukin (IL)-1 β , interleukin-6 and tumor necrosis factor α (TNF α) are the most important inflammatory mediators regulating acute phase protein synthesis in inflammation (1, 3), research on the mechanism of drug metabolizing enzyme regulation in diseases states has focused on these cytokines.

CLINICAL DRUG THERAPY SCENARIOS OF RELEVANCE TO ALTERED P450 REGULATION BY INFLAMMATION

Detailed reviews of cytochrome P450 regulation in inflammation and infection can be found elsewhere (4, 5). In various models and in clinical reports, inflammation or infection are associated with decreased hepatic expression and/or activities of P450s (5). Evidence is beginning to accumulate that intestinal P450s are down-regulated as well (6). Thus for the majority of drugs, the main clinical concern has been that patients on a stable drug regimen who experience an infection or inflammatory episode would have increased exposure to the parent drugs via decreased clearance and/or increased bioavailability (Figure 1), resulting in possible increased incidence of adverse events. Such was the case when an influenza epidemic resulted in decreased clearance of theophylline in children taking the drug for their asthma (7). Other examples have been discussed previously (4, 5). Obviously, the clinical consequences are likely to be the most significant for drugs with a low therapeutic index. For prodrugs that are activated by metabolism, impairment of P450 activities due to inflammation could reduce their therapeutic efficacy, although there are no good examples of this phenomenon to date.

Chronic diseases often have associated inflammation, which is thought to result from a tissue's attempts to adapt to cellular stress or dysfunction (2) and is often less severe than that observed in the acute response to infection or tissue damage. The down-regulation of CYP3A4 in patients with advanced cancer has been reviewed recently (8). Animal model studies suggest that this regulation may be mediated via IL-6 originating from the tumor itself (9). This may be an enzyme-selective regulation, because in a recent small study no effect of cancer on tolbutamide (CYP2C9) clearance was found (10). The reader is referred to a previous review for a discussion of the effects of other chronic inflammatory diseases on drug metabolism in humans (5).

Iatrogenic effects

Interferons (IFN) and proinflammatory cytokines can down-regulate P450 expression in vivo and in hepatocyte cultures, and these mediators are thought to be the main cause of P450 down-regulation in inflammatory states (5). IFNs and IL-2 are used in the therapy of various cancers, and therefore they have the potential to cause drug-drug interactions. Several studies have found that therapy with IFN α or IFN β was associated with decreased P450-dependent drug clearance (11). Overall, different IFN α or β preparations tended to consistently reduce CYP1A2 activities and clearances, whereas effects on other P450s were more variable. In patients with secondary hepatic cancer, treated with different doses of IL-2, dose-dependent reductions in protein levels of CYP1A2, CYP2C, CYP2E1, and CYP3A4 proteins and activities in the range of 40-60% of control were found (12).

Biologics

The last decade has seen the emergence of a large number of drugs that are biological peptides or proteins targeted to the neutralization of growth factors and cytokines, which are used in the treatment of cancers and various inflammatory diseases. As shown in Table I, several of these biological drugs target inflammatory cytokines (or their receptors). TNF α , IL-1 β , and IL-6 are capable of down-regulating expression of multiple P450s in primary human hepatocytes (13), whereas IL-2 regulates hepatocyte P450s indirectly via Kupffer cells (14). In a recent study, Ashino et al found that CYP3A11 mRNA and CYP3A protein and activity were selectively down-regulated to 45% of control in a mouse model of rheumatoid arthritis (15). A single i.v. injection of anti-IL6 antibodies reversed the down-regulation of 3A11 mRNA, protein and activity measured 24 h later (15). This finding suggests another possible clinical scenario in which regulation of inflammation could modulate P450-dependent pharmacokinetics and drug responses: reversal of an inflammatory condition by a biological drug targeting an anti-inflammatory cytokine (Figure 1), which would be predicted to result in increased drug clearance, reduced exposure and diminished clinical efficacy. Such an effect could reflect a primary role of the targeted cytokine in hepatic P450s regulation, or it could be due to a secondary effect due to general resolution of inflammation. No such interactions have been reported in humans to date.

There are reports from animal studies that some drug-metabolizing P450s are unaffected by inflammation, and some are even induced (5, 16, 17). The potential consequences of such regulation would be opposite to those of down-regulation. There is no good evidence, as yet, that this occurs with human drug metabolizing P450s in the liver. However, a study of CYP3A and the drug transporter p-glycoprotein (P-gp) mRNA levels in duodenal biopsies (normal tissue) in pediatric Crohn's disease patients found that CYP3A4 and P-gp mRNAs were higher than in a control group (18).

SPECIFICITY, MECHANISMS, AND MEDIATORS

The facts that a) P450 enzymes can be regulated by multiple cytokines in hepatocyte cultures, and b) that the subsets of P450s regulated by individual cytokines are different (13), suggest that P450s will be differentially regulated in different inflammatory disease states. Therefore the drugs whose pharmacokinetics are affected will vary with the type of disease, or with the biological drug administered. Animal studies support this concept. As shown in Figure 2, the pattern of acute hepatic CYP mRNA regulation in C3H/HeOuJ mouse liver following a single dose of bacterial lipopolysaccharide (LPS) is quite different from that caused by infection with *Citrobacter rodentium*, a model of human infection with enteropathogenic *E. Coli*. Of course, some differences between disease models could depend on the time points selected for observation. However, in the examples in Figure 2, the time points represent those of maximal effect in each model

As reviewed previously (5), the inflammatory down-regulation of P450 enzymes occurs at several levels. For most P450s studied, the decreases in P450 protein expression are preceded or accompanied by decreases in the mRNAs, implicating transcription as a primary mechanism. The transcription factor NF- κ B is a master regulator of inflammation (19), which has been implicated in the regulation of P450s via interaction with their induction mechanisms. Inflammatory stimuli can antagonize the action of the pregnane X receptor (PXR) via binding of the p65 subunit of NF- κ B to the retinoid X receptor (RXR) (20, 21). Thus, other RXR-dependent transcription factors may be antagonized in the same way. NF- κ B binds to the aryl hydrocarbon receptor (AhR), and these two transcription factors can repress each other's function (22). Activation of NF- κ B can also down-regulate the constitutive androstane receptor (CAR) via antagonism of its control by glucocorticoids (23).

All of the preceding effects of NF- κ B affect drug induction mechanisms of P450 genes, and as such they impair the inductive response of P450s to drugs. However, these receptors have little role in the basal or constitutive expression of P450 genes, and so mechanisms of down-regulation of constitutive P450 expression are likely to be different (5). Indeed, we found that LPS treatment down-regulated hepatic P450 expression similarly in PXR-null or wild type mice (24). Nevertheless, we found a role for NF- κ B in the down-regulation of CYP2C11 in rat hepatocytes, via direct binding to the CYP2C11 gene (25). Tindberg et al also described an NF- κ B binding site in intron 2 of the CYP2E1 gene, that functioned as a cytokine-sensitive repressor in rat primary cortical glial cell cultures (26). As reviewed previously, activation of the short form of C/EBP β (LAP) has been implicated in down-regulation of CYP3A4 by IL6 (27), and the down-regulation of various hepatocyte-specific transcription factors also contributes to decreased P450 transcription (5).

Evidence is accumulating that the down-regulation of CYP enzymes in the LPS model of inflammation is mediated via oxidative stress, because treatment with various antioxidants blocks or attenuates the down-regulation of P450s 3A11, 1A1 and 2E1 as well as PXR (6, 28, 29). The Kupffer cell toxin GdCl₃ also prevented down-regulation of PXR and CYP 3A11 (28). Since NF- κ B is a redox-sensitive transcription factor, the oxidant-dependence of the P450 and PXR down-regulation may indicate a role of NF- κ B in CYP3A11 and PXR regulation in this model. However, such a role could be many steps upstream of P450 and PXR regulation, because activation of NF- κ B by LPS via TLR4 is a very early event in the inflammatory cascade (19), triggering activation monocytes and macrophages, including Kupffer cells.

Although transcriptional suppression is a major factor in the down-regulation of many CYPs, there are multiple post-transcriptional effects as well, including regulation of catalytic activity (reviewed in (5)). We recently demonstrated that NO resulting from the inflammatory induction of inducible nitric oxide synthase triggers the ubiquitin-dependent proteasomal degradation of rat CYP2B1, but not CYP2C11 (30, 31). Nitric oxide also down-regulated CYP2B6 but not CYP3A4 or 2E1 (30, 31). More work is needed to determine if this mechanism applies to other P450 enzymes.

BIOMARKERS

The clinical utility of this field of research will be to facilitate rational decisions about adjustment of drug doses, or choice of appropriate therapy, under the scenarios discussed above. Only by understanding the mechanisms of P450 regulation by inflammatory agents, and by knowing the major inflammatory mediators (e.g. cytokines) responsible for regulation of individual enzymes *in vivo*, will we be able to develop and validate biomarkers that could be used to predict the likely effect of inflammation on drug metabolism in a patient or a population.

Such biomarkers might be cytokines themselves, since they are known to regulate P450 enzymes. For example, serum IL-6 correlates with the reduced CYP3A4-dependent clearance in cancer patients (8, 9). The ability of a cytokine to down-regulate a P450 in hepatocyte culture and the fact that the cytokine is correlated with P450 activity in a given disease state does not mean that the cytokine is the principal regulator *in vivo*, or that changing its activity will alter the P450 expression. Illustratively, mice with a targeted knockout of IL-6, IL-1 β or TNF α receptors exhibit unchanged regulation of acute-phase and P450 genes following injection of LPS (32) despite the ability of IL-6, TNF α or IL-1 β to down-regulate P450 expression in cells (5). In likelihood this is because cytokines act redundantly to regulate hepatic gene expression in response to this pleiotropic inflammatory stimulus. On the other hand, genetic deletion of IL-6 does attenuate the down-regulation of

some P450s in mice treated with a subcutaneous irritant (tissue damage model) (32). This suggests that cytokines themselves may be useful biomarkers in certain inflammatory diseases, although this needs to be further substantiated. Clearly there are diseases in which single cytokines will not be useful as biomarkers, and we will need to look for markers that are readouts of the combined actions of cytokines and other inflammatory mediators. These may be plasma proteins, such as acute phase proteins, or they could be other proteomic or metabolomic markers.

CONCLUSIONS

Inflammation associated with infection or other disease states down-regulates multiple P450 enzymes as well as other drug metabolizing enzymes and drug transporters. Good evidence exists that the pattern of regulation differs depending on the disease, and that proinflammatory cytokines are the principal mediators of these effects. This regulation may have consequences not only for the onset of an inflammatory reaction, but also for its amelioration by biologic agents that act via cytokine or cytokine receptor neutralization. More understanding of the mechanisms involved and the *in vivo* contributions of cytokines in different disease states is needed to facilitate our ability to interpret and predict changes in pharmacokinetics in a given disease state.

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Figure 1.

Effect of onset or amelioration of inflammation on hepatic cytochrome P450 expression or activity, and on steady state drug concentrations in plasma. The *left panel*, depicts a patient on a stable drug regimen who becomes afflicted with an acute inflammatory or infectious disease. Down-regulation of the hepatic P450(s) responsible for clearing the drug results in reduced clearance and elevated means steady state plasma concentrations of drug. The *right panel* depicts the theoretical situation of a patient with a chronic inflammatory condition who is on a stable drug regimen. When the patient is treated with an anti-inflammatory drug (e.g. one targeted towards a proinflammatory cytokine), the down-regulation of the relevant P450 enzyme is relieved, drug clearance increases, and means steady state plasma concentrations of drug decrease.

Figure 2.

Comparison of the effects of LPS injection or infection with *Citrobacter rodentium* on hepatic P450 enzyme mRNAs. Data are taken from published studies in which C3H/HeOuJ mice were either infected with *C. rodentium* and killed 6 days later (33), or injected with 1 mg/kg LPS and killed 12 h later (16). The mRNA levels in the respective control groups were set at 1 (dotted line) for each P450 mRNA, and the expression in the treated groups is expressed as a fraction of control. Values are mean $\pm$ S.E.M., *, $p < 0.05$ compared to control.

TABLE 1

Therapeutic proteins targeted towards inflammatory diseases

Drug	Type	Target	Diseases/Indications
Adalimumab	Mab ¹	TNF α	Rheumatoid arthritis
Certolizumab-pegol	Mab, Fab' fragment	TNF α	Crohn's disease
Etanercept	Receptor fragment	TNF α	Rheumatoid arthritis
Infliximab	Mab	TNF α	Rheumatoid arthritis, Crohn's disease
Anakinra	Receptor antagonist	IL-1 receptor	Rheumatoid arthritis
Daclizumab	Mab	IL-2 receptor (α -chain)	Acute organ rejection, asthma, Multiple sclerosis, autoimmune
Tocilizumab	Mab	IL-6 receptor	Rheumatoid arthritis

¹ Mab, monoclonal antibody